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ECHOCARDIOGRAPHIC ESTIMATES OF LEFT VENTRICULAR REMODELING IN MITRAL REGURGITATION ACCORDING TO THE TYPE OF SURGICAL CORRECTION: MITRAL VALVE REPAIR OR REPLACEMENT

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The pathophysiology of chronic primary mitral regurgitation (MR) is primarily based on a degenerative process. Inadequate adaptation of the left ventricle (LV) due to volume loading leads to gradual dilatation and weakness. The only complete therapeutic option in this case is surgical intervention. This study was aimed at evaluating early echocardiographic parameters of LV remodeling in chronic primary MR between two types of operative correction, a mechanical mitral valve replacement (MVR) and mitral valve prosthetic ring annuloplasty (MVA). Using 2D and M-mode echocardiography, a number of variables were measured or calculated. In addition, the variables are assessed according to early postoperative LV dysfunction (LVD). Ejection fraction (EF) was < 50%. Thirty-six asymptomatic patients with primary severe MR (grade 3-4) undergoing surgical correction were included. The LV end-diastolic diameter improved significantly (6.11 \pm 0.9 vs. 5.50 \pm 0.7 cm) in both groups (p < 0.006) after interventions, while there were no significant differences in LV volumes between the groups. Immediate postoperative LV systolic dysfunction showed similar incidence in the groups (43%). A significant distinction between the groups was revealed in patients without LVD, that is, a higher preoperative forward LVEF in MVA compared to MVR patients. Interestingly, the opposite direction of forward LVEF change was seen in LVD between the groups. We can conclude that there are subtle differences in early postoperative echocardiographic parameters between the MVA and MVR procedures, reflecting subtle specificities of early LV remodeling in patients with chronic primary MR.

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Key words: annuloplasty, end-diastolic diameter, ejection fraction, left ventricular dysfunction, end-systolic volume

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Introduction

Mitral regurgitation (MR) is the second most common valvular lesion, with its prevalence rising with age. Considering an increase in population ageing, MR prevalence is likely to increase further (1–4). Mitral regurgitation develops due to a failure of the mitral leaflets during left ventricular

(LV) contraction. It can be classified as primary, related to valve abnormalities, or secondary, due to distortion of LV shape. According to the disease course, MR can present as an acute or chronic disorder. The etiology of chronic secondary MR is either ischemic or non-ischaemic, resulting in annular dilatation and the papillary muscles' displacement, causing mitral valve failure (3–5).

Primary MR is considered a degenerative disease in about two-thirds of all cases, without defined causative factors. Nevertheless, long-term exposure to elevated blood pressure is observed to predispose to a substantial share of these patients. Specifically, each 20 mmHg increment in systolic blood pressure was associated with a 26% higher risk of MR. Similar associations are reported for each 10 mmHg increase in diastolic blood pressure. The effects were mediated directly and secondarily to high BP complications (4).

During the insidious development of chronic primary MR, there is progressive LV dysfunction and a reactive remodelling in an attempt to provide an adequate forward stroke volume (SV).

Initial hemodynamic changes, such as an increase in left atrial (LA) volume, a reduction in forward SV, and a rise in LV preload, further respond by eccentric hypertrophy. The compensation attempt implies the increase in wall thickness and increased LV filling, which normalizes forward SV. However, this is found insufficient to fully compensate for the wall stress (3).

The inadequate hypertrophy is supposed to occur partly because volume overload in MR does not trigger substantial increases in the rate of protein synthesis. Instead, the early wall thickening is due to a decrease in the rate of protein degradation (6). Other mechanisms include altered cytoskeletal changes, an increase in reactive oxygen species, a change in matrix metalloproteinase expression and activation, initiation of inflammatory and apoptotic pathways, and others. Ensuing disruption of the myocardial extracellular matrix architecture results in sliding displacement of cardiomyocytes and cell death. Adversely remodeled and dilated LV progresses to the decompensated MR with a thin myocardial wall and an increase in wall stress (3, 7, 8).

Therefore, surgical repair or mitral valve replacement (MVR) is currently the recommended therapy for severe primary MR, in patients who are surgical candidates. Without proper treatment, severe mitral valve regurgitation can cause abnormal cardiac rhythm and inevitably lead to heart failure (3, 4).

Aim

This study was aimed at evaluating the first week's echocardiographic parameters of LV remodeling between two types of operative correction in patients with chronic primary MR: a mechanical mitral valve replacement (MVR) and mitral valve prosthetic ring annuloplasty (MVA).

Materials and Methods

We conducted a prospective study that included 36 consecutive patients diagnosed as having grade 3-4 MR according to the 2020 American College of Cardiology/American Heart Association (ACC/AHA) quideline the management of patients with valvular heart disease and using appropriate validated techniques (1, 9, 10). The patients were recruited at the Clinic for Cardiac Surgery, University Clinical Center of Serbia (University of Belgrade, Serbia), between 2019-2021.

Inclusion criteria comprised asymptomatic patients with primary severe MR, of non-ischemic and non-rheumatic causes, with a routine transthoracic echocardiography performed with quantification of MR. Excluded patients were those with ischemic cardiomyopathy, acute cardiac events, those who underwent bypass surgery, a percutaneous angioplasty, or had an aortic valve disease, mitral stenosis or other heart diseases.

Criteria for quantitative gradation of severe primary MR (grade 4), based on 2D echocardiography, included: effective regurgitant orifice area (EROA) (2D proximal isovelocity surface area (PISA), mm²) of \geq 40 mm², regurgitant volume (mL/beat) of \geq 60 mL, and regurgitant fraction (%) \geq 50% (1, 9).

Patient-centred and integrative approach to evaluation of a specific lesion causative of MR was applied in accordance with current guidelines. The approach provides prognostic implications and is of vital importance for assessing possibilities of surgical or transcatheter valve repair (1, 10).

Patients were divided into two age-matched groups of those who underwent a MVR with a mechanical prosthesis and those with restrictive prosthetic ring annuloplasty (downsizing of $2.7\pm0.8\,$ ring sizes). As per guidelines, MVR is commonly performed in patients with severe MV disease unsuitable for surgical repair (11).

All patients were routinely assessed by transthoracic echocardiography before and three to four days after the surgical procedure (early follow-up). The obtained echocardiographic parameters were compared between these two periods and between the groups (MVA vs. MVR).

Using 2D and M-mode echocardiography, a number of variables were measured or calculated (through the Teicholz method), including dimensions (end-diastolic (EDD), end-systolic (ESD)) and volumes of the LV (EDV, ESV, SV), thickness of the myocardial wall and septum in diastole. Ejection fraction (EF%) and shortening fraction (FS%) were also evaluated, as well as derived measures of forward LVEF (100 × forward stroke volume/LV EDV), right ventricle systolic pressure (RVSP) and left ventricle wall stress (WS).

We further assessed differences in echocardiographic parameters in relation to an early postoperative LV dysfunction, which is defined as LV EF < 50% after mitral valve surgery.

Statistical Analysis

Results are expressed as mean \pm standard deviation (SD) or median \pm interquartile range (IQR), or percentages, as required. The Wilcoxon signed-rank test, Mann–Whitney U test or independent/paired t-tests were used, based on the normality distribution of data (assessed by the Shapiro–Wilk test). The Pearson correlation coefficient test was also used. A significance threshold was set at p < 0.05. Statistical analysis was carried out using SPSS 25.0 software (SPSS Inc., Chicago, IL, USA).

Results

Out of 36 patients included in the study, 21 (58.3%) underwent MVA, while 15 (41.7%) had MVR intervention. There were 28 (77.8%) males and 8 (22.2%) females, median years of age 66.5 ± 12 . Demographic data and risk factors were

comparable between the groups. Baseline characteristics of the patients are shown in Table 1. There was no significant difference in the type of procedure according to gender or body mass index (BMI). All patients recovered in the postoperative period. Mitral regurgitation grades at discharge were 1.18 ± 0.34 (mean \pm SD).

Early Echocardiographic Parameters of LV Remodeling

There was a significant difference in EF% before and after the MR surgery (57.53 \pm 12.32 vs. 49.78 \pm 10.46, p = 0.000; r = 0.537), as well as in FS% (36.27 \pm 7.23 vs. 30.73 \pm 4.71, p = 0.045; r = 0.668), but with no significant difference between the type of surgical correction.

Forward LVEF values were significantly higher after the procedure (32.67 \pm 10.97 vs. 43.49 \pm 16.77, p = 0.005), but again, similar according to the type of procedure. The postoperative forward LVEF positively correlated with RVSP (r = 0.541, p = 0.025).

End-diastolic diameter of the LV improved significantly (6.11 \pm 0.9 vs. 5.50 \pm 0.7) in both groups (MVA p = 0.000, MVR p = 0.006) (r = 0.654, p = 0.000) after interventions, while ESD measurements remained mostly unaffected (3.85 \pm 1.0 vs. 3.95 \pm 0.9, p > 0.05) (r = 0.754, p = 0.000). There were no differences in the LV dimensions between the groups in this early period. Similarly, left atrial (LA) diameters decreased postoperatively in both groups (5.30 \pm 1.33 vs. 4.60 \pm 0.88, p = 0.02).

We determined a significant difference in the median between EDV, before and after the MR correction (190.46 \pm 59.12 vs. 147.4 \pm 40.14 ml, p = 0.000) (r = 0.701, p = 0.000), but not for end-systolic volumes (67.96 \pm 45.58 vs. 67.95 \pm 34.21 ml, p > 0.05) (r = 0.805, p = 0.000).

Similar findings were obtained for the mean level of SV before and after the surgery (115.95 \pm 34.92 vs. 77.62 \pm 24.53 ml, p = 0.000) in both groups (p < 0.003), but without correlation. There were no distinct differences in EDV, ESV or SV according to the type of MR surgery.

Right ventricular systolic pressure was elevated (\geq 30 mmHg) before (48.9 ± 15.0 vs. 49.6 ± 13.5 mmHg) and after (37.7 ± 8.8 vs. 42.3 ± 9.6 mmHg) the interventions in MVA and MVR groups, respectively, but with no significant difference between the two periods or between the groups. Also, the LV WS remained almost the same in the two periods (116.54 ± 0.65 vs. 116.16 ± 14.92 kdynes/cm², p > 0.05).

After the treatment, the mitral velocity propagation (Vp) recordings were different between the groups, with higher velocity in MVR (1.400 \pm 0.345 vs. 1.681 \pm 0.259 m/s, p = 0.015), which was related to characteristics of mechanical valves.

A Comparison According to Postoperative LV Systolic Dysfunction (LVD)

Out of 36 patients, 8 (22.2%) had EF% lower than 50% prior to the mitral correction and therefore were excluded from analysis of postoperative LVD. Twelve out of 28 patients (42.9%) with adequate preoperative EF developed early LVD, half of them had underwent MVA (6/15) and another half had MVR procedure (6/7) (p > 0.05). There was no significant difference in the number of subjects that developed LVD depending on the type of MR correction.

In total, patients with higher preoperative EDD showed a tendency to develop LVD (6.39 \pm 0.77 vs. 5.95 \pm 0.40, p = 0.06), but with no group difference. Postoperative EDD was also higher in those with LDV (5.45 \pm 0.56 vs. 5.38 \pm 0.39, p > 0.05).

A significantly higher preoperative EDD was determined in MVA patients who progressed to LVD (6.50 ± 0.27 vs. 6.01 ± 0.46 , p = 0.038), as well as in the measurements of postoperative ESD (4.26 ± 0.43 vs. 3.73 ± 0.38 , p = 0.035). In the MVR group, there was a tendency for higher preoperative ESD values and higher postoperative EDV in those who developed LVD (Table 2).

In both groups, a significantly lower postoperative FS% were determined in patients with LVD compared to those with stable LV function, that is, in MVA 23.69 \pm 6.76 vs. 31.79 \pm 4.13%, p = 0.016, and in MVR 25.22 \pm 6.23 vs. 33.11 \pm 3.24%, p = 0.044, respectively.

In total, preoperative forward LVEF was lower in LVD patients (31.45 \pm 13.06 vs. 37.41 \pm 8.34, p > 0.05). There was a significant difference in preoperative forward LVEF measures according to the group in those who did not develop LVD. Specifically, patients MVA with postoperative LV function had higher preoperative forward LVEF compared to MVR patients (38.63 ± $8.73 \text{ vs. } 29.50 \pm 4.14, p = 0.045$). Interestingly, we documented the opposite direction of forward LVEF change related to LVD between the groups. Mean values of forward LVEF were lower in MVA patients who developed LVD compared to those who did not (28.5% vs. 38.63%), while the values were higher in MVR patients with LVD versus those with stable function (35.00% vs. 29.5%).

Table 1. Baseline characteristics of the patients (total)

Gender (male), n (%)	28 (77.8%)			
BMI (kg/m²)	26.72 ± 3.18			
MR duration (months)	12 ± 11			
TA systolic (mmHg)	131.28 ± 15.895			
TA diastolic (mmHg)	80.0 ± 18.0			
Hypertension arterial, n	26 (72.2%)			
Atrial fibrillation, n	21 (58.3%)			
Type 2 diabetes mellitus, n	7 (19.4%)			
Cigarette smoking, n	11 (30.6%)			
BMI – body mass index, MR – mitral regurgitation, TA – tension arterialis				

Table 2. Echocardiographic parameters according to the early postoperative left ventricular dysfunction (LVD) and the type of operative procedure

		LVD	Non-LVD	P value
EDD preop (cm)	1	6.50 ± 0.27	6.01 ± 0.46	p = 0.038
	2	6.28 ± 1.10	5.87 ± 0.32	ns
EDD post (cm)	1	5.63 ± 0.26	5.47 ± 0.35	ns
	2	5.22 ± 0.78	5.27 ± 0.44	ns
ESD preop (cm)	1	4.23 ± 0.39	3.87 ± 0.47	ns
	2	4.13 ± 0.68	3.51 ± 0.48	p = 0.080
ESD post (cm)	1	4.26 ± 0.43	3.73 ± 0.38	p = 0.035
	2	3.90 ± 0.62	3.53 ± 0.37	ns
EDV preop (ml)	1	216.28 ± 77.85	185.11 ± 31.40	ns
	2	207.40 ± 34.59	176.36 ± 31.39	ns
EDV post (ml)	1	174.11 ± 90.12	148.74 ± 20.62	ns
	2	164.03 ± 23.59	134.72 ± 24.9	p = 0.053
ESV preop (ml)	1	100.54 ± 78.28	64.72 ± 21.84	ns
	2	87.15 ± 31.61	66.38 ± 31.61	ns
ESV post (ml)	1	79.29 ± 59.56	72.84 ± 37.15	ns
	2	84.66 ± 29.13	61.68 ± 18.72	ns
FLVEF preop (ml)	1	28.50 ± 16.01	38.63 ± 8.73	ns

	2	35.00 ± 8.80	29.50 ± 4.14*	ns
FLVEF post (ml)	1	39.95 ± 20.61	41.94 ± 17.63	ns
	2	43.17 ± 15.47	48.04 ± 15.57	ns
FS% preop (%)	1	34.86 ± 5.51	35.49 ± 7.62	ns
	2	33.65 ± 7.72	40.25 ± 6.30	ns
FS% post (%)	1	23.69 ± 6.76	31.79 ± 4.13	ns
	2	25.22 ± 6.23	33.11 ± 6.23	ns
RVSP preop (mmHg)	1	56.00 ± 12.99	44.67 ± 16.01	ns
	2	55.17 ± 12.92	50.00 ± 11.73	ns
RVSP post (mmHg)	1	36.80 ± 9.45	34.44 ± 8.92	ns
	2	45.50 ± 10.89	40.64 ± 9.73	ns

^{1 -} mitral valve annuloplasty, 2 - mechanical mitral valve, EDD - end-diastolic dimension, ESD -

end-systolic dimension, EDV – end-diastolic volume, ESV – end-systolic volume, FLVEF – forward LV

ejection fraction, FS - fractional shortening, RVSP - right ventricular systolic pressure

Discussion

Severe MR (4+) is associated with progressive ventricular remodeling that results from chronic volume overload. Several studies demonstrated better survival of these patients when mitral valve operative intervention was performed before the onset of symptoms. However, due to established risks of surgery, only patients with a severe degree of MR are selected for the intervention (12-14). The estimation approach using M-mode-derived dimensions is simple, noninvasive, and successful, which allows it to be recommended as a criterion for intervention in mitral valvulopathy. Moreover, LV diameters, volumes, EF% and wall stress are commonly used to assess LV remodeling process (9).

An individualized consideration needs to be performed when deciding on the type of surgical correction for MR, including both patient-related status and specificities of procedure with its potential adverse effects. Studies report that mitral valve replacement is associated with lower occurrence of valve-related complications but greater rates of thromboembolic events and structural impairment of the valve that reflects on ventricular tethered loop and LV contraction (8, 15, 16).

Despite no significant difference in mortality between MVA and MVR for ischemic mitral valve incompetence by the end of 7-year follow-up in the study by Micovic et al. (17), the 30-day mortality rates were significantly higher in the MVR group (9.6% vs. 5.8%). Similarly, in a metaanalysis, clinical outcomes of repair and replacement for severe ischemic MR showed lower perioperative mortality in MVA patients and no differences in long-term survival. However, MVA was associated with a higher recurrence of MR compared to the MVR procedure (15).

We detected subtle changes in the early postoperative period between the two types of procedures for degenerative severe specifically when comparing mitral valve correction with implantation of annuloplasty ring with MVR using a mechanical valve. Following both types of intervention, EDD and EDV decreased significantly compared to initial values, as well as LA diameter, but these were not distinctly different between the groups. Patients with MVA who progressed to LVD (defined as EF < 50%) had significantly higher preoperative EDD (p = 0.038), while other patients showed the same tendency. Postoperative LVD was associated with higher postoperative ESD in MVA patients, while there was a tendency of higher preoperative ESD in the mechanical valve replacement group.

Left ventricular contractile dysfunction is an early and frequent complication of MR surgery. It interferes with and prolongs LV recovery and influences patients' survival. Nevertheless, the issue of early LVD following mitral valve surgery is still poorly evaluated (14, 18, 19). Despite preoperative EF \geq 60%, it is suggested that there is an ongoing myofibrillar degeneration and diffuse interstitial fibrosis in the myocardium with MR

^{*} p = 0.045 compared to MVA

leading to contractile dysfunction that remains asymptomatic and unrecognised until surgical correction. The mitral valve surgery removes the confounding effects of regurgitant volume, reduces preload but increases afterload pressures, thereby unmasking the actual state of LV function (12, 14, 20).

In a study that evaluated short- and long-term changes in postoperative LVEF after mitral valve repair, preoperative LVEF and ESD were found important in defining these changes. There was a greater decrease in LVEF after repair, the higher the preoperative LVEF was, along with preoperative ESD greater than 40 mm compared to < 40 mm (21).

Forward LVEF was shown to be superior to the total EF in predicting outcomes in MR, with higher risk for adverse events in those patients having forward LVEF less than 50%. A preoperative forward EF less than 40% was found to be associated with the risk of developing LV systolic dysfunction after MR corrective procedure (12). Nevertheless, LVD occurs in patients with previously normal LV function as well (14, 18). This parameter could predict early LVD, 3−4 days after an MR repair, with an optimal cut-off of 31.8% reported in patients with preoperative LVEF ≥ 60%. It also correlated with mitral regurgitant volume and fraction (14).

We determined a significant difference in preoperative forward LVEF values according to the type of intervention in patients with preserved postoperative LV function. Those who underwent annuloplasty presented with higher preoperative forward LVEF than those who underwent valve replacement. Although we did not find statistical significance, our MVA patients with postoperative LVD had lower forward LVEF compared to non-LVD. This change had the opposite direction in MVR patients.

Preoperative forward LVEF of less than 40% accurately predicts postoperative LV dysfunction three months after surgery for chronic organic MR (22). Both our groups with LVD had forward LVEF below this limit. Additionally, the results of MVA patients are comparable to the study of Kim et al., who determined an even lower cut-off of 31% for forward LVEF in those progressing to LVD (14).

Other factors reported to be associated with LVD after MR surgery include enlargement in systolic dimension, midwall and stress-corrected midwall FS%, decrease in RVSP after a repair, preoperative RVSP, LA diameters, global longitudinal strain and global circumferential strain (14, 18, 19, 23).

Similarly to others (14, 21), we detected a significantly reduced postoperative FS% compared to the preoperative in our patients (36.3 vs. 30.7%). A fall in FS% indicates LV systolic dysfunction. Also, LVD was associated with

significantly lower postoperative FS% in both our groups (23.7% in MVA and 25.2% in MVR). It is suggested that midwall FS may represent preoperative intrinsic LV contractility that is not obvious before surgical MR correction due to a compensation mechanism for LV volume overload (14, 21).

Left atrial dimensions decreased after MR correction in both groups. There were slightly lower dimensions of LA in LDV patients in both groups, but still higher than normal (> 4 cm). Left atrial size is a simple parameter affected by MR severity and thus may identify patients who are suitable for early elective valve surgery. Moreover, it is found to be the strongest independent echocardiographic predictor of outcome in severe but asymptomatic MR (23).

The information presented here provides valuable insight into the subtle specificities of early LV remodeling according to the type of operative MR correction. Besides MR correction and prevention of recurrence, types of operative intervention represent a new basis that later on defines long-term outcomes.

Conclusion

We can conclude that there are subtle differences in preoperative and early postoperative echocardiographic parameters between the MVA and MVR procedures of surgical MR correction in patients with chronic primary MR. Forward LVEF values were significantly higher after the procedure in general. Left ventricle EDD improved significantly after the interventions, while no significant differences in LV volumes were determined between the groups.

There was a similar incidence of immediate postoperative LV systolic dysfunction in the groups. Each group had distinct alterations to LVD: a significantly higher preoperative EDD and postoperative ESD were present in MVA patients, while the MVR group showed only a tendency towards higher preoperative ESD and postoperative EDV.

A significant distinction between the groups was revealed in patients without LVD, that is, a higher preoperative forward LVEF in MVA compared to MVR patients. Interestingly, the opposite direction of forward LVEF change was seen in LVD between the groups.

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EHOKARDIOGRAFSKA PROCENA REMODELOVANJA LEVE KOMORE U MITRALNOJ REGURGITACIJI PREMA TIPU HIRURŠKE KOREKCIJE: REPARACIJE ILI ZAMENE MITRALNE VALVULE

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Patofiziologija hronične primarne mitralne regurgitacije (engl. mitral requigitation - MR) uglavnom se zasniva na degenerativnom procesu. Neadekvatna adaptacija leve komore (engl. left ventricle - LV) usled zapreminskog opterećenja dovodi do postepene dilatacije i slabosti. Jedinu adekvatnu terapijsku opciju u ovom slučaju predstavlja hirurška intervencija. Cilj ovog istraživanja bio je da proceni rane ehokardiografske parametre remodelovanje LV-a u hroničnom primarnom MR-u u dvema vrstama operativne korekcije: mehaničkoj zameni mitralne valvule (engl. mitral valve replacement - MVR) i anuloplastici mitralnog zaliska protetskim prstenom (eng. mitral valve annuloplasty – MVA). Ehokardiografske varijable su izmerene ili izračunate korišćenjem 2D i M tehnike. Pored toga, varijable su procenjene u odnosu na ranu postoperativnu disfunkciju LV-a (engl. left ventricular dysfunction - LVD). Ejekciona frakcija (engl. ejection fraction - EF) bila je < 50%. Istraživanje je obuhvatilo 36 asimptomatskih pacijenata sa primarnim teškim MR-om (stepen 3-4) koji su bili podvrgnuti hirurškoj korekciji zalistaka. Krajnji dijastolni prečnik LV-a značajno se poboljšao (6,11 cm \pm 0,9 cm prema 5,50 cm \pm 0,7 cm) u obema grupama (p < 0,006) posle intervencija. Kada je reč o zapreminama LV-a, nisu zabeležene značajne razlike između grupa. Neposredna postoperativna sistolna disfunkcija LV-a pokazala je sličnu incidenciju u grupama (43%). Značajna razlika između grupa uočena je kod pacijenata bez LVD-a, odnosno zabeležen je veći preoperativni prednji LVEF kod pacijenata sa MVA nego kod pacijenata sa MVR-om. Nasuprot tome, kod pacijenata sa LVD-om uočen je suprotan smer promene prednjeg LVEF-a. Može se zaključiti da postoje suptilne razlike u ranim postoperativnim ehokardiografskim parametrima između MVA i MVR procedura koje odražavaju suptilne specifičnosti ranog remodelovanja LV-a kod pacijenata sa hroničnim primarnim MR-om.

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Ključne reči: anuloplastika, krajnji dijastolni dijametar, ejekciona frakcija, disfunkcija leve komore, end-sistolni volumen

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